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The effect of sleep restriction on laser evoked potentials, thermal sensory and pain thresholds and suprathreshold pain in healthy subjects

Siv Steinsmo Ødegård [a,*], Petter Moe Omland [a], Kristian Bernhard Nilsen [a,c,d], Marit Stjern [a,b], Gøril Bruvik Gravdahl [a,b], Trond Sand [a,b]

[a] Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology, MTFS, N-7489 Trondheim, Norway
[b] Norwegian National Headache Centre, Section of Neurology, St. Olavs Hospital, N-7006 Trondheim, Norway
[c] Department of Work Psychology and Physiology, National Institute of Occupational Health, Oslo, Norway
[d] Department of Neurology, Section for Clinical Neurophysiology, Oslo University Hospital – Ullevål, Oslo, Norway

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HIGHLIGHTS

- Randomized blinded study on the effects of sleep restriction on laser evoked potentials (LEP) amplitude, LEP-habituation, pain threshold and suprathreshold pain in healthy subjects.
- Sleep restriction reduced LEP-amplitudes and thenar cold pain thresholds.
- The results suggest that the observed hyperalgesia after sleep restriction might be caused by cognitive or perceptual mechanisms, rather than sensory amplification.

ABSTRACT

Objective: Sleep restriction seems to change our experience of pain and reduce laser evoked potential (LEP) amplitudes. However, although LEP-habituation abnormalities have been described in painful conditions with comorbid sleep impairment, no study has previously measured the effect of sleep restriction on LEP-habituation, pain thresholds, and suprathreshold pain.
Method: Sixteen males and seventeen females (aged 18–31 years) were randomly assigned to either two nights of delayed bedtime and four hours sleep (partial sleep deprivation) or nine hours sleep. The study subjects slept at home, and the sleep was measured with actigraphy both nights and polysomnography the last night. LEP, thermal thresholds and suprathreshold pain ratings were obtained the day before and the day after intervention. The investigator was blinded. ANOVA was used to evaluate the interaction between sleep restriction and day for each pain-related variable.
Results: LEP-amplitude decreased after sleep restriction (interaction $p = 0.02$) compared to subjects randomized to nine hours sleep. LEP-habituation was similar in both groups. Thenar cold pain threshold decreased after sleep restriction (interaction $p = 0.009$). Supra-threshold heat pain rating increased temporarily 10 s after stimulus onset after sleep restriction (interaction $p = 0.01$), while it did not change after nine hours sleep.
Conclusion: Sleep restriction reduced the CNS response to pain, while some of the subjective pain measures indicated hyperalgesia.
Significance: Since LEP-amplitude is known to reflect both CNS-pain-specific processing and cognitive attentive processing, our results suggest that hyperalgesia after sleep restriction might partly be caused by a reduction in cortical cognitive or perceptual mechanisms, rather than sensory amplification.

1. Introduction

Although a nociceptive effect of sleep restriction was demonstrated in an experimental study as early as 1934 (Cooperman et al., 1934), there are still uncertainties about the nature of this

* Corresponding author. Tel.: +47 97772989.
E-mail address: siv.steinsmo@gmail.com (S.S. Ødegård).

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relationship (Azevedo et al., 2011; Haack and Mullington, 2005; Kundermann et al., 2008, 2004; Onen et al., 2001; Roehrs et al., 2006; Schuh-Hofer et al., 2013; Smith et al., 2007, 2005; Tiede et al., 2010). From previous studies it seems that sleep restriction enhances our subjective experience of pain, including reduced pain thresholds, but reduce the brain's reaction to pain as demonstrated by laser evoked potential (LEP) amplitudes (Azevedo et al., 2011; Tiede et al., 2010).

However, because these studies have considerable methodological variations, e.g. regarding the type of sleep restriction, it is difficult to explain the neurophysiological mechanism behind this apparently contradictory observation. By extending the LEP- and pain thresholds protocol with paradigms reflecting responses to prolonged pain, i.e. also measuring LEP-habituation and temporal summation of suprathreshold heat pain, we might detect sleep restriction-typical patterns. Such patterns might shed more light on the physiology behind the effects of sleep restriction on pain.

Suprathreshold pain paradigms may reflect temporal summation of pain, and give information about central mechanisms of pain hypersensitivity (Granot et al., 2006). Only a few studies have evaluated the effect of sleep restriction on suprathreshold pain and with varying methods, e.g. to a fixed-intensity laser stimulus (Azevedo et al., 2011; Tiede et al., 2010), as pain score to a cold-pressor conditioning stimulus (Smith et al., 2007), as a heat pain tolerance threshold (Onen et al., 2001) or as a pain score to consecutive pin-pricks for wind-up evaluation (Schuh-Hofer et al., 2013). Generally, results suggest that sleep restriction also might cause suprathreshold hyperalgesia. Since generalized (multi-site) hyperalgesia often suggest central mechanisms of pain hypersensitivity, we used two sites (cephalic and upper extremity) for suprathreshold and for pain threshold determination.

Since habituation is a physiological mechanism that protects individuals from responding to repeated stimuli of moderate magnitude and low significance (Coppola et al., 2013), it is interesting that abnormally decreased LEP-habituation has been described in several painful conditions like migraine (Di Clemente et al., 2013; Valeriani et al., 2003) and fibromyalgia (de Tommaso et al., 2014). Furthermore, as epidemiological studies indicate that there is a causal relationship between insomnia and several painful disorders (Boardman et al., 2006; Canivet et al., 2008; Gupta et al., 2007; Hoogendoorn et al., 2001; Kaila-Kangas et al., 2006; Lyngberg et al., 2005; Odegard et al., 2011; Siivola et al., 2004), it would be interesting to find out whether these two observations are related or not. Specifically, if lack of sleep in healthy individuals result in LEP-habituation abnormalities, it might indicate that sleep loss could be the explanatory mechanism for the observed decreased LEP-habituation in migraine and fibromyalgia. As far as we know, no previous study has investigated the effect of sleep restriction on LEP-amplitude habituation.

As we aimed to compare psychophysical pain thresholds with pain-related CNS-responses, most specifically elicited with laser-induced skin heating, the thermal modality was deemed most suitable. This approach is in line with recent interest in more naturalistic sleep restriction-protocols (Finan et al., 2013). As such, a main aim was to investigate how two nights with sleep restriction affected LEP-amplitude and LEP-habituation. A second major aim was to study how sleep restriction affected thermal pain thresholds and suprathreshold heat pain responses. Thermal detection thresholds were also included as control variables to check for unspecific effects of sleep restriction on the somatosensory system, e.g. related to alertness or attention. Hence, it was also a third general aim to compare several variables, reflecting different aspects of thermal pain and sensory physiology, to explore possible sleep restriction-specific abnormality-patterns.

2. Methods

2.1. Study participants

Study participants were recruited through intranet advertisement within our Hospital and University. The study participants were ⩾18 years old, free of migraine or frequent (⩾3 days/month) tension type headache and otherwise healthy (except mild asthma and allergies). Subjects using drugs that could affect neurological, vascular or muscular function, having any history of alcohol or drug abuse, being pregnant or breastfeeding were not included.

From the 80 subjects who responded to the study advertisement, 33 students (16 males and 17 females), with a mean age of 22.9 (SD = 2.8, range = 18–31) were included in the study (Fig. 1). Before entering the study, subjects completed a general health

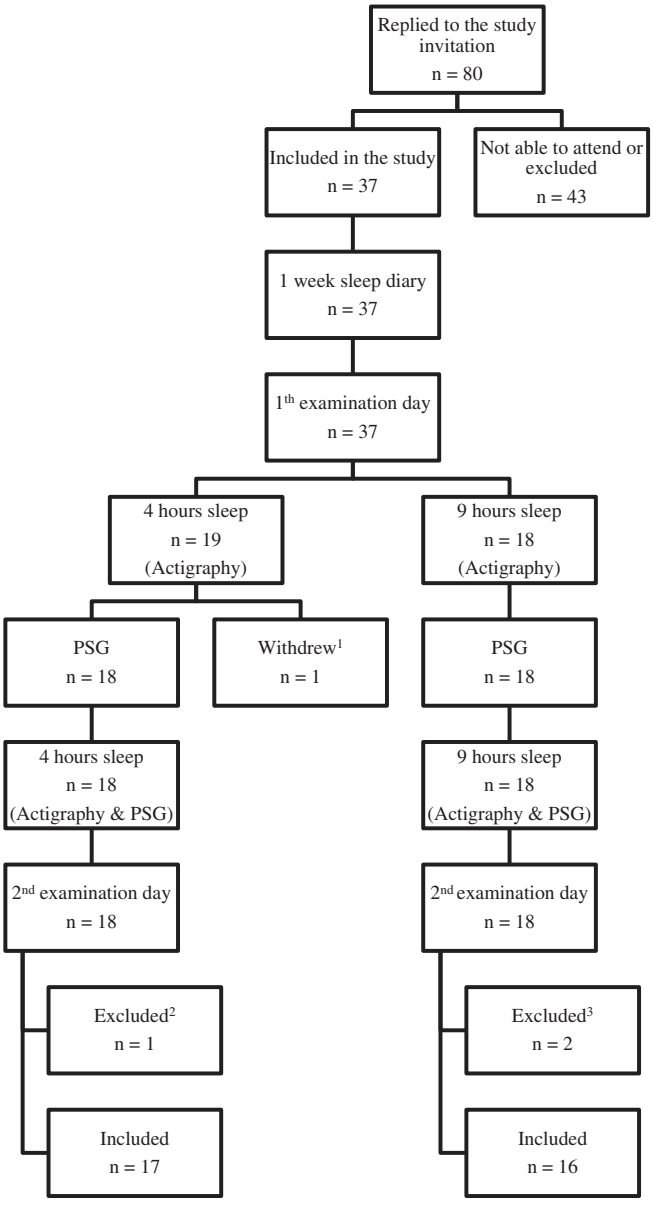

Fig. 1. Flowchart for the participants in the study. [1]: One subject withdrew from the study after the first examination day because of personal reasons. [2]: One subject in the four hours sleep group was excluded from the statistical analysis because of neurological disease. [3]: Two subjects in the nine hours sleep group was excluded from the statistical analysis; one because of frequent headache and one because of limited cooperation with unreliable threshold estimates.

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questionnaire during a telephone interview regarding inclusion and exclusion criteria. The study participants signed a written informed consent, and after completing the two examination days they received 500 NOK (approximately 70 Euro) to cover expenses. The study was approved by the Regional Committee for Research Ethics.

2.2. Procedure

The study participants were asked to sleep as normal before entering the study. They kept a sleep diary one week before the first examination day and throughout the study. On the first examination day (Day 1), the participants came to the laboratory after normal sleep. At the end of Day 1 they were randomly assigned to two groups concerning sleep length, balanced for gender, by receiving a sealed envelope with information to sleep for either four hours or nine hours. The four hours group was told to delay their bedtime to approximately 3 am while the nine hours group subjects should go to bed around 10 pm. They were instructed not to tell the operator about their sleep length. The study subjects slept at home, and sleep length was controlled with actigraphy both nights and polysomnography (PSG) the last night before the second examination day (Day 3) (Fig. 1).

As described in Fig. 1, 37 subjects completed the first examination day. 19 were randomized to four hours sleep, and 18 were randomized to nine hours sleep. In the four hours sleep group, one subject withdrew after the first examination day for personal reasons. Furthermore, two subjects (one in each group) were excluded from the statistical analyses because of a previously undisclosed Charcot Marie Tooth syndrome and frequent headaches respectively. We also excluded one subjects in the nine hours group because of inability to cooperate during thermal threshold testing, causing unreliable and outlying data (Fig. 1). However, these exclusions caused a slight gender distribution asymmetry (Table 1).

Table 1
Baseline characteristic of the study participants randomized to four and nine hours sleep for two successive nights; mean (SD).

	4 h sleep group	9 h sleep group
Number of participants	17	16
Gender (% female)	47	56
Age (years)	22.7 (3.2)	23.1 (2.4)
Height (cm)	174.9 (7.4)	169.9 (10.2)
BMI (kg/m^2)	24.0 (3.8)	23.3 (4.3)
Insomnia score[1] (0–12)	4.12 (0.86)	4.38 (1.82)
Breathing difficulty score[2] (0–8)	0.88 (1.11)	1.0 (1.03)
Sleep length week before[3] (min)	449 (47)	458 (50)
Sleep latency week before[4] (0–3)	1.9 (0.5)	1.6 (0.5)
ESS	8.6 (4.4)	8.3 (3.4)
KSQ-sum	9.2 (2.0)	9.8 (1.5)
Tiredness after test (VAS 0–10)	6.9 (2.4)	5.5 (3.4)
Sleep length during study[5] (min)	234 (46)	446 (36)
Pain-60[6] arm (°C)	46.2 (2.8)	47.2 (2.7)
Pain-60[6] temple (°C)	45.7 (3.1)	47.3 (2.9)
Average energy level (J) used in LEP test	4.4 (0.4)	4.4 (0.6)

SD = standard deviation, h = hours, BMI = body mass index, ESS = Epworth Sleepiness Scale, KSQ = Karolinska Sleep Questionnaire, VAS = visual analog scale, C = Celsius, J = Joule, LEP = laser evoked potentials.

[1] Insomnia as a sum-score from three KSQ-questions: During the last three months difficulty falling asleep at night (0–4) + several awakenings during the night (0–4) + wake up to early and were not able to fall asleep again (0–4).

[2] Sum of two KSQ-questions about heavy snoring (0–4) and apnoea's (0–4).

[3] Sleep length week before based sleep diary, mean sleep length per night (min) the week prior to first examination day.

[4] Categorized as 0: short, 1: within 30 min; 2: 30–90 min.

[5] Sleep length based on actigraphy the first night and PSG the second night (mean).

[6] Suprathreshold heat pain threshold at baseline (60% of worst pain imaginable).

Subjects were given a standard meal before the tests. At the end of the first examination day, the participants completed a sleep questionnaire which included the Karolinska Sleep Questionnaire (KSQ) (Akerstedt et al., 2008; Engstrøm et al., 2011) and the Epworth Sleepiness Scale (ESS) (Beiske et al., 2009; Johns, 1991). Tiredness after completing all tests was reported by a visual analog scale (VAS; 0–10) on Day 1 and Day 3. The first author was responsible for collecting and processing the data and blinded regarding what sleep group the study subjects had been randomized to, until the statistical analysis.

2.3. Actigraphy

The actigraph (Actiwatch 7.0, Cambridge Neurotechnology, Cambridge), worn on the dominant hand, recorded movement in 30 s epochs, while the estimated sleep duration was calculated by the software (Tahmasian et al., 2010). Bed times (''lights off'') and wake-up times (''lights on'') were noted, and later used as an aid in the calculation of sleep duration.

2.4. Polysomnography

PSG was recorded by an experienced technician using a Notta recorder (EEG Technology Int.bv, 6092 NM Leveroy, The Netherlands) and analyzed with Stellate Harmonie software (Stellate, Montreal, Quebec, Canada). Eight electroencephalographic (EEG) electrodes were placed according to the International (10–20) system (Jasper, 1957) at F3, F4, C3, C4, P3, P4, O1, O2 plus Pz reference and Cz ground. Electrooculografic (EOG) electrodes applied two cm laterally and, respectively, two cm above and below the right and left lateral eye cantus. EOG-reference electrodes were applied to the left (A1) and the right (A2) mastoids respectively. Surface electromyography (EMG) was recorded from the submental and left anterior tibial muscles. Respiration and circulation was measured with a three-point oronasal thermistor, piezo-electric bands around thorax and abdomen (Ultima Respiratory Effort Sensor™, crystals, Breabon Medical Corporation, Ontario, Canada), a body position sensor, (Ultima Body Position Sensor™, Breabon Medical Corporation, Ontario, Canada), an infrared index finger device for oximetry, and two electrocardiographic (ECG) electrodes. Sleep stages and arousals were scored by visual analysis according to the American Academy of Sleep Medicine (AASM) guidelines (Iber et al., 2007), with one exception: C3/C4 replaced F3/F4 regarding EEG-amplitude measurements. The latter because our software was released before the AASM 2007 guidelines was published, and was therefore set up with C3-A1 and C3-A2 as default channels. In our experience, the impact of using C3/4 is minimal in young adults due to their generally larger SWS amplitude than older adults (Novelli et al., 2010). Periodic limb movements (PLMs) were automatically scored (Iber et al., 2007), as were apneas and hypopneas followed by a manual correction (American Academy of Sleep Medicine, 1999).

2.5. The examination days

The neurophysiological examinations lasted approximately four hours. Subjects had been told to refrain from alcohol for 24 h, and from caffeine, smoking, exercise, liquids (water was allowed) and food for eight hours before the examination day. Most participants met at 8 am in the morning, while four from the four hours sleep group and six from the nine hours sleep group, were examined in the afternoon (six met 12.30 pm and the rest met between 13 and 16 pm). Thermal thresholds, suprathreshold pain sensitivity and LEP were recorded. The time of investigation was identical both days. The facility, test sequence order and operator were the same both test days within and across study subjects.

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2.6. Thermal thresholds

Thresholds for cold detection (CDT), heat detection (HDT), cold pain (CPT) and heat pain (HPT) were measured with a manually held rectangular 25 × 50 mm, Peltier element thermode (MSA, Somedic Sales AB, Stockholm) (Heldestad et al., 2010) at two sites: Thenar of the left palm and the left forehead above the eye brows. A switch in the right hand was pressed as soon as they felt cool, heat or onset of pain respectively. A brief training session was completed before the actual test. CDT, HDT, CPT and HPT were repeated four times. The baseline temperature was set to 32 °C, the rate of temperature change was set to 1 °C per second and the intervals between each stimulus varied randomly between four and six seconds. The maximum and minimum temperatures were set to 55 °C and 5 °C respectively.

2.7. Supra-threshold temporal summation heat-pain test

The thermode was first placed on the left forearm (5 cm proximal to the wrist) and afterwards over the left temple. The participants were instructed to use a numeric rating scale (NRS) with the extremes: 0 = no pain and 10 = worst pain imaginable. First, the temperature that evoked 60% pain (NRS = 6) for each individual was determined (Granot et al., 2008). The temperature was 32 °C at baseline, changed with a rate of 1 °C per second, and reached a set temperature plateau that lasted for seven seconds. NRS was reported, and the temperature returned to baseline. Second, starting with 45 °C as the set temperature NRS was reported for at least three different set temperatures (with one minute intervals in-between) until a temperature was perceived as NRS = 6. The intention with the procedure was not revealed and participants were told to rate pain every time they felt a change in its intensity. Third, the temperature was increased from the baseline temperature with a rate of 1 °C per second and reached a plateau at the NRS-6 temperature for 30 s. The study participants reported pain NRS every time they felt a change in pain intensity, and the ratings at 10, 20 and 30 s were recorded in order to detect temporal summation of pain (Granot et al., 2008).

2.8. Laser evoked potentials

Painful heat stimuli were generated by an infrared neodymium:yttrium-aluminum-perovskite (Nd:YAP) laser (STIMUL 1340, DEKA M.E.L.A SRL, Florence, Italia), with an energy ranging from 2 to 6.5 J, duration 6 ms, and a wavelength of 1.34 μm. The laser beam was transmitted through an optic fiber and the diameter was set to 8 mm (~50 mm^2). Before the test, skin temperature was measured. Silver disc electrodes were placed on Fz, Cz, Pz (referred to nose), T3 and T4 (referred to Fpz), Cz (referred to A1 and A2). The main analysis channel was pre-selected to be Cz-nose according to the international federation of clinical neurophysiology (IFCN) guidelines (Cruccu et al., 2008). The other channels were used as back up to account for inter-individual variation in field topography and to improve detectability of waves. The patient ground was placed between Cz and Pz. To detect eye blinking, two electrodes were placed below and above the right eye. The bandwidth was 0.2–100 Hz, sampling rate was 1000 Hz, the amplifier sensitivity was ± 100 μV and the impedance was kept below 5 kΩ. Participants lay comfortably and relaxed on a bench with protective goggles and ear shields. Single-response rejection rate (RR) was defined as the percentage of accepted single responses that did not cross the fixed amplifier rejection level at ±90 μV.

The laser beam was directed at the right dorsal hand (distal to the extensor line on the wrist, proximal to the metacarpophalangeal joint, and between metacarpal bones II-IV. Stimuli were given at 6–10 s intervals to minimize central habituation (Iannetti et al., 2005), and the laser beam was moved ⩾ 10 mm between each stimulus to minimize peripheral habituation and avoid damage to the skin (Iannetti et al., 2005). First, the individual thresholds for pinprick pain were identified. Starting at 2 J and increasing with 0.5 J steps every second stimuli until the threshold was found. Threshold was defined as the intensity where pain was felt at least in one of the two trials. If pain was felt they were to differentiate between burning pain and pinprick pain, and if the latter, rate the pain with a NRS (with the extremes: 0 = no pain and 10 = worst pain imaginable).

The intensity equal to two times the pinprick threshold was used during LEP-recordings, corresponding to 4.5 J s for the majority of subjects. Two consecutive blocks with 20–40 stimuli were applied (40 stimuli per block were used for the first five participants, but due to the uncomfortable nature of the test we continued with 20 stimuli in each block, which was sufficient to register a stable LEP curve). Due to intra-individual variability 4.5 J generated too much pain in eight subjects or too little pain in three subjects and the energy had to be adjusted up or down to a final stimulus intensity ranging between 3.0 and 6.5 J. During LEP recording each pain stimulus was rated with NRS to ensure a stable attention level (Iannetti et al., 2005). The same energy level was used both test days. The study participants were not told that the energy was constant.

2.9. Data analysis

The KSQ included three questions used about insomnia: How often during the last three months have you experienced: 1) difficulty falling asleep at night, 2) several awakenings during the night and 3) waking up too early and being unable to fall asleep again. Two questions regarding sleep-related breathing problems were also included; 1) Loud snoring and 2) Breathing pauses in sleep. The response alternatives were: 0 = never, 1 = seldom, 2 = sometimes, 3 = several times a week, 4 always. Scores for the questions were added together (insomnia score 0–12, apnoea score 0–8).

Thermal thresholds were expressed as the difference between the system-recorded baseline temperature (approximately 32 °C) and mean threshold for CDT, HDT, CPT and HPT at thenar and forehead respectively (CDTd = baseline – CDT, HDTd = HDT – baseline, CPTd = baseline – CPT, HPTd = HPT – baseline).

Mean NRS ratings at 10, 20 and 30 s of constant heat stimuli (forearm and temple) were calculated to measure temporal summation for suprathreshold pain.

LEP peaks were identified visually based on their latencies and polarity in the Cz – nose derivation. We calculated the peak-to-peak amplitude of N2P2 in blocks 1 and 2. We further recorded the subjective feeling of pain (NRS) during block 1 of the LEP test.

Table 2
Polysomnographic variables from the second study night after one night of either sleep restriction or unrestricted sleep; mean (SD).

	4 h sleep group	9 h sleep group
Total sleep time (min)	247 (76)	410 (89)
Sleep latency (min)	3.4 (3.0)	54 (64)[1]
Stage N1 sleep (min)	23 (14)	43 (13)
Stage N2 sleep (min)	78 (37)	170 (53)
Stage N3 sleep (min)	88 (35)	106 (28)
REM sleep (min)	58 (24)	91 (36)
Arousal index (per h)	7.2 (3.5)	9.5 (3.1)
AHI (per h)	0.52 (0.85)	0.40 (0.57)
PLMI (per h)	2.6 (5.3)	2.1 (3.0)

h = hours, AHI = apnoea–hypopnea index (AASM 2007A), PLMI = periodic limb movement index.

[1] Three subjects in the 9 h sleep group, scheduled for bedtime at 10 am, had prolonged sleep latencies.

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2.10. Statistics

Skewed data were transformed with appropriate power-functions to obtain normality before statistical analysis (Kolmogorov–Smirnov test). Applied transforming functions have been added to legends in Tables 3–6. Repeated measures analysis of variance (ANOVA) was used to investigate the possible interaction between sleep restriction and pain-related variables. The preplanned tests of interest were the interaction between "Day" (Day 1 vs. Day 3) and "Sleep" (four hours sleep group vs. nine hours sleep groups). To investigate whether the N2P2-amplitude and its habituation were affected by lack of sleep we used the within-subjects factors: "Block" (block 1 vs. block 2) and "Day" and the between-subject factor: "Sleep". To evaluate the interaction between thermal pain thresholds and sleep restriction the dependent variables included in the analyses were: "CPTd thenar", "HPTd thenar", "CPTd frontal" and "HPTd frontal". Similar ANOVAs were performed for thermal detection thresholds. We further analyzed the subjective pain scores during the suprathreshold temporal summation test using the dependent variables: "Pain forearm (NRS)" and "Pain temple (NRS)" and the within subject factors "Time" (ratings at 10, 20 and 30 s) and "Day". Degrees of freedom for "Time" were Huyhn-Feldt corrected for non-sphericity. Mauchly's test of sphericity indicated that the assumption of sphericity had been not violated for other conditions. If an interaction was found, this was further evaluated with the Student's paired *t*-test as a descriptive tool. Corrections for multiple variables have not been done because these variables represent different hypotheses and differing aspects of pain physiology. As such, corrected statistics would be too conservative, i.e. testing the "universal null-hypothesis" which is of limited interest (Perneger, 1998). However, in light of the general type I error risks, the study should mainly be regarded as exploratory regarding the secondary aims.

The power in a two-group Student's *t*-test with 33 subjects was 74% to detect a moderately large effect = 0.9 SD. Two-sided *p* values <0.05 was regarded as significant. Statistical analyses were performed with the Predictive Analytics Software (PASW), Statistics version 17.0 or SYSTAT version 11, by Inc., an IBM Company (Chicago, IL, USA).

3. Results

3.1. Characteristics of the study subjects

There were no group differences regarding gender, age, height, BMI, insomnia, sleep length, breathing difficulty, sleepiness or sleep quality (Table 1).

3.2. The effect of sleep restriction on sleep-variables

Subjects randomized to four hours sleep slept on average 3.9 h per night during the study, while subjects randomized to nine hours sleep slept on average 7.4 h per night (Table 1). Tiredness after the final test was increased in the four hours group (Table 1). None of the study subjects had an AHI $\geqslant 5$, and there was no difference in mean AHI or PLMI (Table 2). Three subjects in the unrestricted sleep group, scheduled for bedtime at 10 am, had prolonged sleep latencies above two hours; hence, mean sleep latency was high. Subjects randomized to four hours sleep also had less stage N1 sleep, stage N2 sleep and REM sleep, while SWS reduction was of lower magnitude (Table 2).

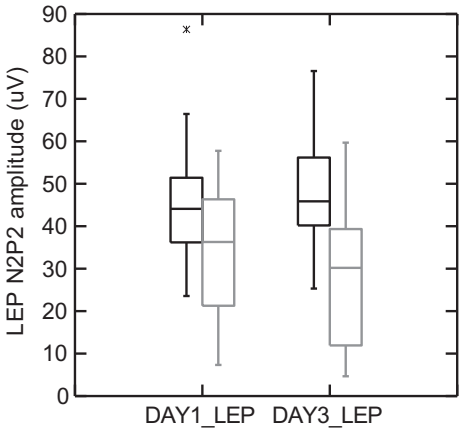

Fig. 2. Box-plot of peak-to-peak laser evoked potentials (LEP) N2P2-amplitude on Day 1 and Day 3 (block 1 and block 2 average; Cz-nose derivation). Median, 25 and 75 percentile box and range (and one outlier plotted as an asterisk) are shown. Subjects were randomized to either sleep restriction (four hours delayed onset sleep; grey right box) or unrestricted nine hours sleep (black left box). LEP N2P2-amplitude is reduced after sleep restriction (ANOVA Sleep × Day interaction $p = 0.02$).

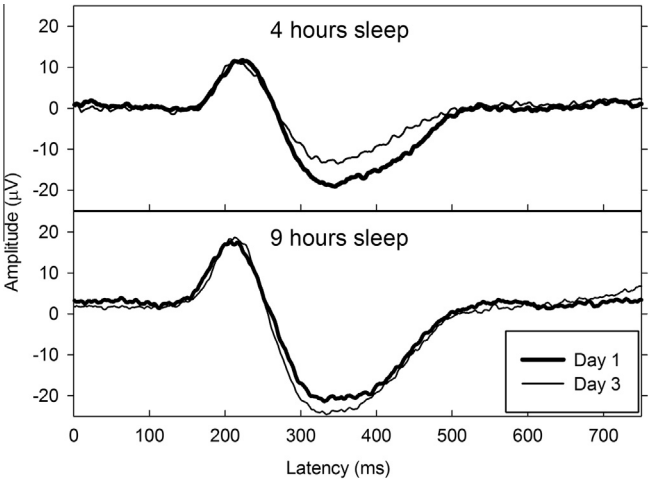

Fig. 3. Grand average laser evoked potentials (LEP) from the Cz-nose derivation. Baseline (Day 1) waveforms are indicated by thick lines. Measurements after restricted sleep (4 h) and unrestricted (9 h) sleep on Day 3 are indicated by thin lines. Peak-to-peak N2P2-amplitude was reduced after 4 h sleep and increased after 9 h sleep.

3.3. Laser evoked potentials

Habituation of the LEP responses was found, as the mean N2P2-amplitude was in general smaller in Block 2 than in Block 1 (block *p*-value <0.0005). However, Day × Block × Sleep interaction was not significant (Table 3), indicating no effect of sleep restriction on LEP-habituation.

The peak-to-peak N2P2-amplitude distributions on Day 1 and Day 3 are demonstrated in box-plots (Fig. 2). The Day × Sleep interaction was significant ($p = 0.02$; Table 3) because the four hours sleep group had a lower N2P2-amplitude on Day 3 compared to Day 1 ($t = -2.5$, $p = 0.03$), as opposed to no change between Day 1 to Day 3 among subjects in the nine hours sleep group ($t = 1.4$, $p = 0.2$; Fig. 2). A significant baseline N2P2-amplitude difference the four hours sleep group and the nine hours sleep was also observed (Table 3). LEP grand means are shown in Fig. 3.

There was no difference in single-response rejection rate (RR) during averaging at Day 1 and Day 3 in either sleep group (Day × Sleep interaction $p = 0.1$; data not tabulated). Pain ratings (NRS)

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Table 3
Laser evoked potential (LEP) N2P2 amplitude at baseline (Day 1) and after intervention (Day 3) in the sleep restricted (4 h) and unrestricted (9 h) groups.

	4 h sleep group	9 h sleep group
Day 1 Block 1 (uV)	36.1 (15.8)	49.7 (19.3)
Day 1 Block 2 (uV)	29.5 (18.6)	41.1 (13.7)
Day 3 Block 1 (uV)	31.3 (17.8)	53.8 (13.5)
Day 3 Block 2 (uV)	27.5 (17.4)	44.9 (15.3)
Sleep *F* (*p*)		9.4 (0.004)
Block *F* (*p*)		27.2 (<0.0005)
Block × Sleep interaction F (*p*)		1.7 (ns)
Day × Sleep interaction F (*p*)		5.8 (0.02)
Day × Block × Sleep interaction F (*p*)		0.6 (ns)

Repeated measures ANOVA (no transformation), *F*-statistic (df 1,31) and *p*-value. h = hours, ns = not significant.

Table 4
Thermal pain thresholds at baseline (Day 1) and after intervention (Day 3) in the sleep restricted (4 h) and unrestricted (9 h) groups.

	Thenar		Frontal	
	4 h sleep group	9 h sleep group	4 h sleep group	9 h sleep group
Cold pain threshold (CPTd)				
Day 1	16.8 (6.8)	19.7 (6.6)	11.7 (7.7)	15.8 (7.8)
Day 3	14.7 (5.5)	20.8 (6.2)	11.4 (6.5)	16.5 (8.3)
Sleep *F* (*p*)	5.3 (0.029)		3.2 (ns)	
Day × Sleep interaction F (p)	10.0 (0.004)		1.7 (ns)	
Heat pain threshold (HPTd)				
Day 1	10.4 (3.6)	12.2 (4.4)	8.7 (3.1)	11.1 (3.4)
Day 3	11.0 (3.0)	12.6 (3.4)	8.9 (3.3)	11.4 (3.6)
Sleep *F* (*p*)	2.4 (ns)		6.2 (0.019)	
Day × Sleep interaction *F* (*p*)	0.1 (ns)		0.0 (ns)	

Repeated measures ANOVAs *F* (df 1,31) and *p*-value. Transformed data (power = 2). h = hours, ns = not significant, CPTd = 32 °C − CPT. HPTd = HPT − 32 °C.

Table 5
Thermal detection thresholds at baseline (Day 1) and after intervention (Day 3) in the sleep restricted (4 h) and unrestricted (9 h) groups.

	Thenar		Frontal	
	4 h sleep group	9 h sleep group	4 h sleep group	9 h sleep group
Cold detection threshold (CDT)				
Day 1	1.9 (0.6)	1.8 (0.7)	1.0 (0.3)	1.1 (0.5)
Day 3	2.0 (1.0)	1.8 (0.6)	1.0 (0.3)	1.1 (0.5)
Heat detection threshold (HDT)				
Day 1	2.1 (0.8)	2.3 (1.5)	1.2 (0.5)	1.2 (0.7)
Day 3	2.1 (0.8)	1.9 (0.8)	1.3 (0.5)	1.2 (0.7)

Repeated measures ANOVAs for CDT and HDT, transformed data (power = 0.125): all *F* (df 1,31) were non-significant. h = hours.

during LEP were not affected by sleep deprivation (Day × Sleep interaction $p = 0.6$; data not tabulated).

3.4. Thermal threshold test

ANOVA revealed a significant interaction between day and sleep for CPTd at thenar ($p = 0.009$; Table 3) with a lower cold pain threshold at thenar after sleep restriction compared to baseline ($t = -3.12$, $p = 0.007$) while no change was found in the nine hours sleep group ($t = 1.42$, $p = 0.18$). Significant effects of sleep restriction were neither found for heat pain thresholds (Table 4) nor thermal detection thresholds (Table 5).

3.5. Supra-threshold pain test

A significant Day × Time × Sleep interaction was found for suprathreshold forearm pain ($p = 0.01$) because the pain score was high early (at 10 s) in the Day 3 session for the sleep restriction group, thereafter decreasing to values that were comparable to the nine hours sleep group (Table 6). Sleep restriction did not affect suprathreshold temple pain (Table 6).

4. Discussion

In this neurophysiological study on healthy young adults, sleep restriction was associated with decreased N2P2-amplitude, while no change in amplitude was observed in the group randomized to nine hours sleep. It should be noted that there was a significant difference in N2P2-amplitude between the four hours sleep group and the nine hours sleep at baseline as well. Since subjects were randomized, the group difference at baseline is interpreted as a random difference. Importantly, the differences between groups increased from baseline, i.e. the finding is not caused by this baseline difference (for instant not consistent with passive "regression towards the mean"). The reduce N2P2-amplitude after sleep restriction is in accordance with two previous studies (Azevedo et al., 2011; Tiede et al., 2010). Tiede et al. (2010) found that one night with sleep restriction lead to a significant N2P2-amplitude reduction, and Azevedo et al. (2011) found sleep restriction to increase the LEP-threshold.

LEP is considered to be an objective measure of cognitive and perceptual pain processing (Baumgartner et al., 2006; Garcia-Larrea et al., 2003; Iannetti et al., 2005; Legrain et al., 2002), and LEP also reflects attentional resources allocated to processing of pain (Lorenz and Garcia-Larrea, 2003). A reduced LEP-amplitudes after sleep restriction could in theory be related to increased habituation since it is seemingly decreased in a painful disorder like migraine for various modalities (Coppola et al., 2013) although blinded studies have failed to confirm this regarding the visual domain (Omland et al., 2013). Lack of LEP-habituation has been reported for painful disorders like fibromyalgia (de Tommaso et al., 2014), migraine, (Di Clemente et al., 2013; Valeriani et al., 2003) and medication-overuse headache (Ferraro et al., 2012). We observed habituation as expected in both groups, and as such, we found no effect of sleep restriction on LEP-habituation. Hence, the reported lack of LEP-habituation in migraine (Valeriani et al., 2003) and fibromyalgia (de Tommaso et al., 2014) might not be related to the impaired sleep-quality that is commonly reported by patients with headache (Engstrom et al., 2013a,b, 2014) and painful disorders (Smith and Haythornthwaite, 2004).

Interestingly, apparently contrary to the reduced LEP-amplitude after sleep restriction, the study participants reported higher pain ratings to the stimuli in both the study by Azevedo et al. (2011) and Tiede et al. (2010). In more details, Azevedo et al. (2011) reported increased subjective pain to a 300 mW laser stimulus after two days of total sleep deprivation, while Tiede et al. (2010) reported increased laser pain ratings after partial sleep deprivation; a difference that was significant only under distracted attention. In agreement with the neutral condition in the latter study, we found that pain ratings during LEP were not different between the four hours sleep group and the nine hours sleep group.

Although sleep restriction did not seem to enhance the feeling of pain inflicted by laser stimuli, we found a hypersensitivity to cold pain at thenar in the four hours sleep group while no change was observed for non-nociceptive thermal detection. Other studies have also found that sleep restriction may affect thermal pain thresholds (Kundermann et al., 2008, 2004; Schuh-Hofer et al., 2013). Furthermore, Roehrs et al. (2012) have found extended

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Table 6
Suprathreshold NRS[1] pain levels in the arm and temple at baseline (Day 1) and after intervention (Day 3) in the sleep restricted (4 h) and unrestricted (9 h) groups.

	Arm		Temple	
	4 h sleep group	9 h sleep group	4 h sleep group	9 h sleep group
Day1				
Pain 10 s	5.6 (1.2)	5.6 (1.1)	4.9 (1.3)	5.1 (1.4)
Pain 20 s	6.2 (1.6)	6.3 (1.6)	4.8 (1.9)	5.5 (1.9)
Pain 30 s	6.5 (1.9)	6.4 (2.3)	4.7 (2.2)	5.4 (2.6)
Day 3				
Pain 10 s	6.9 (1.4)	5.3 (1.3)	5.4 (1.5)	5.5 (1.3)
Pain 20 s	5.9 (2.2)	5.4 (1.3)	5.0 (1.9)	5.5 (1.8)
Pain 30 s	5.9 (2.6)	5.7 (1.8)	4.8 (2.1)	5.0 (2.4)
Sleep[2]	0.9 (ns)		0.7 (ns)	
Day × Sleep interaction F (p)[2]	3.5 (0.07)		0.3 (ns)	
Day × Time × Sleep interaction F (p)[3]	5.6 (0.01)[4]		0.6 (ns)[5]	

Repeated measures ANOVA with transformed data (power = 2). F (df 1,31)[2] or F (df 2,62)[3] and p-value. Huynh-Feldt epsilon = 0.83[4] and 0.92[5]. [1]NRS = numeric rating scale with the extremes 0 cm = no pain and 10 cm = worst pain imaginable. h = hours, ns = not significant.

bedtime (ten hours) to reduce pain sensitivity to heat stimulus (measured by finger withdrawal latency) among healthy volunteers, as compared to unrestricted sleep. In opposition to these results, Onen et al. (2001) found a lower threshold for mechanical, but not thermal, pain. Hence, the latter authors suggested that thermal tests might be less sensitive than pressure-pain tests regarding the ability to detect changes in pain threshold.

We also found a non-generalized effect of sleep restriction and hypersensitivity to suprathreshold heat pain rated 10 s after onset of the continuous heat pain stimuli at the forearm. However, it should be emphasized that sleep restriction was not associated with suprathreshold heat pain hypersensitivity after 20 or 30 s and that pain ratings during LEP of the hand did not indicate a general and lasting hypersensitivity after sleep restriction. Still, this early hypersensitivity to suprathreshold pain may partially explain why pain-scores to phasic suprathreshold laser stimulation were increased after sleep restriction (Azevedo et al., 2011), as opposed to the lack of increase after a tonic cold pressor stimulus (Smith et al., 2007). Smith et al. (2007) found reduced Diffuse Noxious Inhibitory Control (DNIC; currently termed Conditioned Pain Modulation - CPM) after forced awakening, but not after sleep restriction. It is difficult to conclude about the effects of sleep deprivation on suprathreshold pain in general due to different methods applied in these studies. However, it may seem that either a phasic stimulus, use of total (not partial) sleep deprivation or attentional distraction is required for suprathreshold hyperalgesia.

Haack et al. (2012) found that temporal summation of pain was reduced in subjects with primary insomnia, possibly caused by enhanced activation of pain-inhibitory processes. In our study we also observed slightly decreasing suprathreshold pain at 20 and 30 s with ongoing pain in the four hours sleep group. However, we interpret this pattern as a short-lasting hyperalgesia caused by sleep restriction, not as reduced temporal summation. Partly in accordance with our results, Schuh-Hofer et al. (2013) found that one night of total sleep deprivation did not increase temporal summation, although hyperalgesia to heat, cold and blunt pressure was observed. A similar hyperalgesia has also been observed in insomnia (Haack et al., 2012).

The present study has some limitations. A larger number of participants could have given sufficient power to detect smaller effects, including possible small gender differences, although this was not our present aim. However, the actual sample size was sufficient to detect moderately sized effects of probable clinical significance. Type I errors should also be considered, and our new findings should be independently confirmed before generally accepted. Another tentative limitation is the lack of objective post-test sleepiness measures, e.g. by PSG-determined recovery sleep, actigraphy or the Karolinska Sleepiness Scale (Kaida et al., 2006), but these measures were not deemed necessary since we measured actual sleep length with actigraphy. Also, increased VAS tiredness was documented in the four hours sleep group.

The fixed test-order could have affected the estimated effects of sleep restriction, but probably to the same degree in both groups, leaving the group-difference constant. Our priority was to minimize variability within the groups in order to preserve statistical power; hence a fixed order was chosen for the present study.

Another possible limitation is that a few subjects were examined in the afternoon. However, previous studies suggest that diurnal effects on LEP and pain thresholds are minimal (Bachmann et al., 2011). In addition, the imbalance was small between groups (four vs. six afternoon sessions); hence this is an unlikely source to bias. Also, all our tests activated thermal pain receptors. As pointed out by Roehrs et al. (2006), the effect of sleep loss might be unique to the class of nociceptors.

Strengths of the present study include a randomized and blinded design, identical facility, instructions and operator both days. Any order-effect is accordingly equal in the two groups. Also, in the present study, warm and cool detection thresholds were added to control for unspecific effects, but general trends towards changed alertness were not found, as detection thresholds did not differ between groups.

In addition, PSG from the second night was performed to document adherence to protocol and the effect of restricted sleep. However these PSG-data can accordingly not be used to evaluate baseline group differences. Since the target sleep time for the unrestricted night was set to nine hours, implying forced bedtime around 22 pm, and some participants had actual habitual patterns with bedtimes around midnight, sleep latency and N1 percentage was higher in this PSG than it would have been in any normal night. Indeed, diary-recorded sleep latency was not different between groups.

Type and length of sleep restriction has varied a lot, but most previous studies have also included nights with total sleep deprivation (Table 7). However, Haack and Mullington (Haack and Mullington, 2005) found significantly increased bodily pain after two nights with four hours sleep and others have also reported increased pain ratings after partial sleep deprivation (Roehrs et al., 2006; Smith et al., 2007; Tiede et al., 2010). Partial sleep deprivation techniques may results in more relevant insight on how sleep and pain are related (Finan et al., 2013). Hence, we chose to deprive subjects partially to achieve more realistic model for usually happens in daily life. Since subjects slept at home, adherence would probably also be better with partial than total sleep deprivation.

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SWS-rebound during the second night could possibly be able to mask the effects on pain of SWS-deprivation (Onen et al., 2001). However, real SWS-rebound, including any cognitive effect thereof, was probably minimal, as N3 was about 88 min in the four hours sleep group and 101 min in the nine hours sleep group, and about 80% of N3 is expected to occur within the first half of sleep in young adults (Chan et al., 2013).

SWS may seem to be more important for pain regulation than REM sleep (Azevedo et al., 2011; Onen et al., 2001). In contrary to this belief, Roehrs et al. (2006) found REM sleep deprivation to affect the perception of pain while Smith et al. (2005) found that increased suprathreshold pain score was associated with REM sleep length. In the present study there was a relatively larger reduction in REM sleep compared to SWS in the restricted group. This follows naturally from the expected preponderance of SWS early and REM late in the night. We had only one PSG-night and further studies are needed to understand how sleep architecture, e.g. the REM/SWS ratio, may influence pain.

Regarding how lack of sleep might lead to hyperalgesia, several theories have been proposed. Sleep restriction might increase inflammatory mediators and sensitize nociceptors (Haack and Mullington, 2005). Another possibility is that lack of sleep disrupts top-down inhibitory pain control mechanisms (Kundermann et al., 2004; Smith et al., 2007). However, these theories do not explain why sleep loss seems to affect "objective" (i.e. LEP) and "subjective" (i.e. pain thresholds and ratings) pain responses in opposite directions. If the enhanced subjective feeling of pain after sleep restriction were caused by a sensory amplification alone, we would have expected an increased LEP-response amplitude as well (Azevedo et al., 2011). It is therefore more likely that the sleep restriction is related to hyperalgesia through cognitive or perceptual mechanisms (Azevedo et al., 2011).

Sleep restriction reduces our alertness and attention (Tiede et al., 2010), partly mediated by the effect on dopaminergic signaling in the ascending reticular activating system (Finan et al., 2013). Hence, since lack of sleep both reduces our capability to direct attention to and withdraw attention from painful stimuli (Tiede et al., 2010), we suggest that this mechanism may explain the apparent opposite effects from sleep restriction seen on LEP compared to psychophysical pain measures. This is a view supported by the conception that LEP-amplitudes mainly are related to the saliency of the stimulus, as advocated by Mouraux and Iannetti (2009). The reduced LEP-amplitudes after sleep restriction may thus be considered a result of reduced attentional reorientation towards painful stimuli.

Table 7
Summary of published papers on the influence of sleep restriction on the experience of pain.

Study	Participants (*n*/ gender)	Intervention	Control sleep length	Pain test	Results
Azevedo et al. (2011)	CO: 10♂ IG: 1) 9♂, 2) 9♂	1) Total SD 2 n 2) REM SD 4 n	Normal sleep 2 n (lights off 11 pm & lights on 8 am)	LEP-threshold VAS	Total SD increased LEP-threshold and VAS pain ratings
Haack and Mullington (2005)	CO: 14♂, 8♀ IG: 12♂, 6♀	12 n of 4 h sleep	12 n of 8 h sleep	Bodily pain	Bodily discomfort slightly increased across days of sleep restriction
Kundermann et al. (2004)	CO: 5♂, 5♀ IG: 6♂, 4♀	Total SD 1n × 2 (2 d normal sleep in between)	Undisturbed sleep (lights off 10–11 pm & lights on 7–8 am)	Thermal thresholds Thermal pain thresholds	Total SD decreased heat pain threshold
Kundermann et al. (2008)	CO: 7♂, 3♀ IG: 4♂, 5♀	6 n of total SD	Undisturbed sleep	Thermal thresholds Thermal pain thresholds	Total SD reduced heat pain thresholds
Onen et al. (2001)	Cross-over 9♂	6 n x2 (⩾2 weeks in between): N1 = adaptation N2 = baseline N3 = total SD (40 h) N4–5 = REM/SWS deprivation N6 = recovery		Tolerance towards mechanical- & heat pain	Total SD decreased the tolerance towards mechanical pain, and recovery after SWS deprivation increased the tolerance towards mechanical pain
Roehrs et al. (2006)	Cross-over with 2 SD groups: 1) 1♂, 6♀ 2) 2♂, 4♀	4 n: 1) N1 = 8 h in bed N2 = 4 h in bed N3 = 0 h in bed 2) N1 = 8 h in bed N2 = 2 h in bed N3 = 9.5 h in bed with REM ↓ N4 = 9.5 h in bed with nREM ↓		Time to response (finger-withdrawal) when exposed to heat pain	4 h vs. 8 h: ↓ time to response 2 h vs. 4 h: ↓ time to response REM↓ vs. nREM↓: ↓ time to response
Schuh-Hofer et al. (2013)	Cross-over 14 (8♂, 6♀)	1 n of total SD		Spontaneous pain-complaints Thermal threshold Mechanical threshold Pressure pain threshold Dynamic mechanical allodynia Temporal summation Paradoxal heat sensation	Total SD: hyperalgesia to cold, heat, blunt pressure, and mechanical pain to pinprick stimuli
Smith et al. (2007)	CO: 12♀ IG: 2) 10♀ 3) 10♀	7 n: N1–2 = 8 h N3–5 = 1) control, 2) forced awakening or 3) restricted sleep N6 = Total SD N7 = recovery sleep	Undisturbed sleep	Spontaneous pain-complaints Mechanical pain threshold Diffuse Noxious Inhibitory Controls	Forced awakening: decreased pain inhibition and increased spontaneous pain.
Tiede et al. (2010)	Cross-over 10 (8♂, 2 ♀)	Partial SD 1 n		LEP amplitude (N1 & N2P2) VAS	Partial SD reduced the LEP-amplitude and increased VAS pain ratings

CO = control group, IG = intervention group, n = night, d = day, N1 = night 1, N2 = night 2, N3 = night 3, N4 = night 4, N5 = night 5, N6 = night 6, N7 = night 7, h = hours, REM↓ = REM interruption, nREM↓ = non-REM interruption, SD = sleep deprivation.

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